

## **Aldose reductase studied by comparative analysis of neutron scattering, X-ray ultra-high resolution and QM electron density maps and molecular dynamics**

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*Abstract:* Aldose reductase is currently one of the best characterized macromolecular structures known, with X-ray ultra-high resolution (0.66Å), MAD (0.9Å) and more recently a neutron scattering structure (2.2Å) available. Yet, the nature of the proton pathway leading to substrate production remains complex to elucidate. Neutron scattering and X-ray electron density maps reveal a large amount of density along the Lys77-Tyr48 axis. This observation can be reproduced by reconstructing the electron density using QM/MD techniques. The reconstruction points to the rapid reorganization of a proton wire extending from His41 to His110 as the origin of the unusual density. This process may be key to our understanding of the enzymatic mechanism of this enzyme, suggesting the pair Asp43-Lys77 as an essential element in the catalytic mechanism. This work has been funded in part with funds from the NCI-NIH (Contract No. NO1-CO-12400). The contents of this publication do not necessarily reflect the views or policies of the DHHS, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.